Subtle killers and sudden death: Genetic variants modulating ventricular fibrillation in the setting of myocardial infarction

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Chapter 1
Outline of the thesis
Sudden cardiac death

Sudden cardiac death (SCD) is defined as a sudden unexpected death of cardiac origin occurring within an hour after onset of symptoms. SCD is a major contributor to mortality in the general population, accounting for almost 20% of total mortality and 50% of cardiac mortality in industrialized countries \(^1,2\). Although it may strike at all ages, it primarily occurs in adults. Here the most common arrhythmia causing SCD is ventricular fibrillation (VF) which most commonly arises in cardiac pathologies that are associated with coronary artery disease (CAD). Sequela of CAD which present with VF-predisposing substrate include first acute myocardial infarction (MI) and structural cardiac alterations such as myocardial dilatation and fibrosis (scar formation) in those with prior MI.

Considering the size of the problem of SCD, substantial efforts have been made to develop risk-stratification methods aimed at identifying individuals at increased risk of SCD. Thus far, risk stratification has mostly revolved around clinical indicators for increased risk. For example, reduced left ventricular ejection fraction (LVEF) is useful to identify risk of SCD in patients with diagnosed ischemic heart disease. However, while LVEF as a clinical indicator of SCD risk has been widely implemented in clinical practice, and has been clearly successful, it is not universally applicable since 40-50% of SCDs occur in individuals without previously recognized heart disease \(^3,5\). Clearly other means of risk stratification are required to predict risk of SCD in this large group of patients to prevent such catastrophic events. Among possible risk stratifies are genetic factors. This approach has become possible because of the current understanding of the genome and the development of new cost-effective methodologies for genetic testing at the molecular level.

Genetic factors predisposing to Sudden Cardiac Death

The search for genetic modifiers of SCD risk is supported by the consistent identification of family history of SCD as an independent risk factor of SCD in epidemiological studies. Evidence for existence of a heritable component for risk of SCD was first found in two studies published in the late 1990s \(^6,7\). In the Paris Prospective I study \(^7\) a long-term (> 20 years) cohort study of > 7,000 middle-aged French men, parental history of SCD was a predisposing factor for SCD. The relative risk of SCD increased by 1.8-fold if one parent had SCD, and by 9.4-fold if both parents had SCD \(^7\). In a case–control study published by Friedlander and colleagues, a positive family history of early-onset SCD (aged < 65 years) was associated with a 2.7-fold increased risk of SCD after adjustment for other risk factors and family history of MI \(^6\). Following the
first evidence from these two initial studies, our group initiated the AGNES study (Ar-rhythmia Genetics in the NEtherlandS Study) specifically to analyze risk factors for VF in patients with a first acute ST-segment elevation MI (STEMI). Our group identified SCD among first-degree relatives as an independent risk factor for VF (Odds ratio: 2.72) by comparing STEMI patients who also had VF with STEMI patients who did not have VF. This finding rationalized the search for genetic determinants of VF risk in the AGNES case-control set which formed the major aim of this thesis. By focusing on patients presenting with this specific phenotype (VF in the setting of STEMI), we aimed at enriching the homogeneity of pathways leading to VF across the patients studied in order to favor genetic locus identification. Establishment of the AGNES case-control set coincided with the advances in genetic technology and emergence of techniques that allowed for the large (genome-wide) assessment of genetic variants. The genetic architecture of risk of VF in the setting of a first acute MI is expected to be complex as assumed for other multi-factorial disorders affecting older individuals.

Aim of thesis and outline

The aim of this thesis is to identify genetic risk factor for the occurrence of VF in the setting of an acute STEMI. Studies were conducted primarily in the AGNES case-control set.

The first section of the thesis consists of two reviews (Chapters 2 and 3) that introduce the topic and review the literature pertaining to the genetic perspectives of SCD/VF.

In Chapter 4 and Chapter 5 of the thesis, I employed an approach entailing genome-wide association study (GWAS) of common genetic variants for the identification of genetic loci predisposing to VF. The GWAS method, which was enabled by the mapping of genetic variation in the general population within the HapMap and the 1000 Genomes projects, has in recent years been broadly applied to uncover genetic determinants of risk in a wide range of complex diseases and traits. GWAS has provided a large number of new loci associated with complex traits and diseases and has thus provided new biologic insight into their mechanisms. GWAS tests millions of common single nucleotide polymorphisms (SNPs; variants present in more than 5% of the population) to identify those that are associated with the disease or trait of interest. The GWAS conducted in the AGNES case-control set in Chapter 4 constitutes the first published GWAS on the phenotype of SCD/VF. Chapter 5 describes our second GWAS effort in the AGNES study, conducted on an extended number of AGNES cases and controls. In this chapter, alongside GWAS, we undertook complementary strategies in which we harnessed available data on expression quantitative trait loci
(eQTL) in human heart and also conducted pathway-based analysis. The eQTL approach is based on the fact that most loci identified by GWAS reside in non-coding regions of the genome and are therefore expected to exert their effect on the associated trait through regulation of gene expression. We therefore examined the effects of SNPs (uncovered in AGNES GWAS) on the expression level of genes located within 1 Mb spanning the VF-associated lead-SNP, with the aim of identifying possible causal genes at the associating loci. In another approach in this chapter, we selected 911 independent candidate SNPs previously identified as eQTLs in human heart and tested them for association with VF. The aim here was to prioritize SNPs that are already recognized to be putatively functional by virtue of their effect on gene expression in human heart, and to investigate whether they may increase risk of VF. In Chapter 5, in an attempt to approach the exact biological mechanism, we also performed a pathway analysis to investigate whether the genes in the vicinity of SNPs found to associate with VF through GWAS in AGNES are enriched in any pre-existing biological pathway. In this chapter, we additionally extracted SNPs previously associated with SCD in published candidate gene studies and assessed their association with VF.

Chapter 6 and 7 in this thesis are dedicated to gene discovery through intermediate phenotype approach. Phenotypes that are considered risk factors for SCD are often referred to as “intermediate phenotypes” of SCD and genetic modifiers of these phenotypes are thus expected to also determine the risk of SCD. The use of the intermediate phenotype approach in the dissection of genetics of VF may increase the chances of genetic locus discovery as it considers candidate SNPs in pathways that are biologically plausible for VF. An intermediate phenotype that is highly relevant for VF is heart rate and electrocardiographic (ECG) indices of conduction and repolarization. These quantifiable traits are heritable and several studies have linked them to the risk of VF/SCD. In the last 8 years a number of large-scale GWAS studies have identified genetic modifiers of these parameters in large samples of the general population. In Chapter 6 of this thesis we investigated the role of candidate SNPs previously found to be associated with heart rate and ECG indices of cardiac conduction and repolarization and assessed them for possible modulatory effects on risk of VF in the setting of acute MI in the AGNES case-control set.

Another phenotype that we regarded as an intermediate phenotype for VF was inflammation. Several lines of evidence from population based, case-control, and experimental studies support the hypothesis that a pro-inflammatory status may increase risk of arrhythmia and SCD. In Chapter 7 of this thesis, we described a second candidate SNP approach that we undertook by selecting SNPs previously found to associate with inflammatory biomarkers in the general population.

The overarching aim of this thesis is thus the identification of new genetic loci that predispose to VF in the setting of acute MI.
References


